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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.

EXAMINER	
ART UNIT	PAPER NUMBER
	4

DATE MAILED:

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No.	Applicant(s)	
	09/632,149	CUTHBERTSON, R. ANDREW	
	Examiner	Art Unit	
	Quang Nguyen, Ph.D.	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 13-22 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 13-22 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

a)☐ All b)☐ Some * c)☐ None of the CERTIFIED copies of the priority documents have been:

1.☐ received.

2.☐ received in Application No. (Series Code / Serial Number) _____ .

3.☐ received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. & 119(e).

Attachment(s)

15) ☒ Notice of References Cited (PTO-892)
16) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
17) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
18) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
19) ☐ Notice of Informal Patent Application (PTO-152)
20) ☐ Other:

DETAILED ACTION

The numbering of claims is not in accordance with 37 CFR 1.126 which requires the original numbering of the claims to be preserved throughout the prosecution. When claims are canceled, the remaining claims must not be renumbered. When new claims are presented, they must be numbered consecutively beginning with the number next following the highest numbered claims previously presented (whether entered or not).

Misnumbered claims 1-10 have been renumbered 13-22, respectively.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 13-22 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The factors to be considered in the determination of an enabling disclosure have been summarized as the quantity of experimentation necessary, the amount of direction or guidance presented, the state of the prior art, the relative skill of those in the art, the predictability or unpredictability of the art and the breadth of the claims. *Ex parte*

Forman, (230 USPQ 546 (Bd Pat. Appl & Unt, 1986); *In re Wands*, 858 F.2d 731, 8 USPQ 2d 1400 (Fed. Cir. 1988)).

The claims are drawn to a method of treating a genetic ocular disease comprising incorporating exogenous nucleic acid into an *in situ* ocular cell under conditions permissive for the uptake of said exogenous nucleic acid, said exogenous nucleic acid encoding a protein associated with said ocular disease, whereby said exogenous nucleic acid is expressed, and thereby treating said genetic ocular disease. The claims are drawn to the same method wherein said genetic ocular disease is autosomal retinitis pigmentosa, autosomal dominant retinitis punctata albescens, butterfly-shaped pigment dystrophy of the fovea, adult vitelliform macular dystrophy, Norrie's disease, blue cone monochromasy, choroideremia and gyrate atrophy. Claim 22 is directed to the same method wherein a patient having an ocular disease suffers from a lysosomal storage disease.

The specification discloses that following superficial epithelial debridement (surgical removal of superficial epithelial cells) and upon topical application of β-galactosidase expressing recombinant adenoviral vector on the corneal surface for 30 minutes, extensive β-galactosidase expression was noted in the corneal epithelial cells of treated rats. Similarly, the specification teaches that upon administering replication-deficient β-galactosidase expressing recombinant adenoviral vector into anterior chamber of the eye, positive staining of the majority of cells lining the posterior surface of the cornea or the corneal endothelial cells was observed for treated rats. Similar injection of the recombinant adenoviral vector into the vitreous humor of the eye of

treated rats, positive staining of some of the cells of the choroid was detected for β-galactosidase expression.

The above evidence is noted and considered. However, the evidence can not be extrapolated to the instant claimed invention which is drawn to a method of treating various genetic ocular diseases and an ocular disease associated with the lysosomal storage disease. The nature of the instant claimed invention falls within the realm of gene therapy. The specification is not enabled for the instant claimed invention because at the effective filing date of the present application (October 31, 1994), gene therapy is an immature and highly unpredictable art. It has been noted that there are several factors limiting an effective gene therapy, and these include suboptimal vectors, a lack of long term and stable gene expression, and an efficient gene delivery to target tissues or cells. The specification fails to provide guidance and example demonstrating that any genetic ocular disease or a non-genetically based ocular disease associated with a lysosomal storage disease could be treated by the instant claimed method to yield any therapeutic result. Relevant information regarding to specific vector constructs comprising specific transgenes to be utilized for a particular genetic ocular disease and appropriate dosages of recombinant vectors to be used are not provided by the instant specification. Applicant's specification fails to provide an adequate written description for one of skill in the art to carry out the claimed method, and without the specifics provided by the instant specification for a method of treating any of numerously claimed genetic ocular diseases and an ocular disease associated with lysosomal storage

disease, it would have required undue experimentation for one of skill in the art to use the claimed invention. The courts have stated that:

> A specification need not disclose what is well known in the art. See, e.g., Hybridtech Inc. v. Monoclonal Antibodies, Inc., 802 F.2d 1367, 1385, 231 USPQ 81, 94 (Fed. Cir. 1986). However, that general, oft-repeated statement is merely a rule of supplementation, not a substitute for a basic enabling disclosure. It means that the omission of minor details does not cause a specification to fail to meet the enablement requirement. However, **when there is no disclosure of any specific starting material or of any of the conditions under which a process can be carried out, undue experimentation is required; there is a failure to meet the enablement requirement that cannot be rectified by asserting that all the disclosure related to the process is within the skill of the art**. It is the specification, not the knowledge of one skilled in the art, that must supply the novel aspects of an invention in order to constitute adequate enablement.

(Genetech Inc. v. Novo Nordisk A/S, 42 USPQ2d 1005 (CAFC 1997) (emphasis added).

Regarding to the breadth of the claims encompassing the expression of any and all protein associated with a genetic ocular disease or an ocular disease associated with a lysosomal storage disease, the specification fails to provide evidence showing that a therapeutically effective amount of said protein could be achieved by the claimed method. Even in the most recent review on available gene delivery systems, Wivel & Wilson stated that "One of the major challenges still confronting the field is the design of more efficient vectors. The gene delivery systems being used today will undoubtedly be seen as crude when compared with future developments. It is unlikely that there will ever be a universal vector, but rather there will be multiple vectors specifically designed for certain organ sites and certain diseases.....It will be necessary to do much more fundamental research in cell biology, virology, immunology, and pathophysiology before

vectors can be significantly improved." (pages 498-499 in Summary section of Hematol. Oncol. Clin. North Am. 12:483-501, 1998). Presumably, the utilized vectors of the instant claimed invention are far from being optimal to yield effective therapeutic levels of desired proteins. Moreover, the specification fails to address issues such as the fate of delivering and uptake of exogenous nucleic acid, the fraction of exogenous nucleic acid taken up by targeted cells, the level of mRNA produced, the stability of the recombinant protein produced, the proper recombinant protein's compartmentalization and its bioactivity. These factors differ dramatically based on which recombinant protein being produced, and the desired therapeutic effect being sought. Therefore, the level of gene expression, its duration and its *in vivo* therapeutic effects are not always predictable, and hence they can not be overcome by routine experimentation.

The breadth of the claims encompass the use of any and all vectors for delivering exogenous nucleic acid to an *in situ* ocular cell, such as retrovirus and herpes simplex virus vectors. It is noted that in many of the claimed genetic ocular diseases wherein primarily differentiated photoreceptors express mutated genes, for example mutated opsin, the β subunit of rod cGMP phosphodiesterase, peripherin/*rds* and others in retinitis pigmentosa, the specification fails to provide guidance for one of skill in the art on how an effective delivery of an exogenous nucleic acid in the form of a retrovirus vector could be achieved in such postmitotic cells in order to achieve any therapeutic effect, since retroviral vectors require target cell proliferation for gene transfer. At about the effective filing date of the present application, Li et al. (Investigative Ophthalmology and Visual Science 35:2543-2549, 1994) noted that although replication-deficient

herpes simplex virus 1 (HSV-1) may hold promise for gene transfer to postmitotic neurons, but the current versions of HSV-1 based vectors are cytotoxic, and the difficulty in obtaining a high titer HSV-1 for an efficient gene transfer (See column 2, second paragraph, page 2543 and column 2, second paragraph, page 2547).

With respect to the scope of the claimed invention encompassing genetic ocular diseases caused by dominant mutated genes, for examples some forms of autosomal dominant retinitis pigmentosa, autosomal dominant retinitis punctata albescens, butterfly-shaped pigment dystrophy of the fovea, the specification also fails to provide direction and example demonstrating that the dominant mutational effects could be overcome through the expression of a corresponding wild type protein coded by the delivered exogenous nucleic acid in the claimed method. Especially, in view of the excess presence of mutated gene products in the autosomal dominant diseases.

Accordingly, due to the lack of guidance and examples provided by the instant specification regarding to the treatment method for various genetic ocular diseases and an ocular disease associated with a lysosomal storage disease, the unpredictable nature of the gene therapy art, and the breadth of the claims, it would have required undue experimentation for one skilled in the art to make and use the claimed invention.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 13-22 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 13 and its dependent claims (14-21) are incomplete, because the claimed method lack a step or steps linking the steps of (a) incorporating exogenous nucleic acid into an in situ ocular cell, (b) the uptake of said exogenous nucleic acid, and (c) the expression of said exogenous nucleic acid, to the recited preamble "treating a genetic ocular disease".

Similarly, claim 22 also lacks a step or steps linking the steps of (a) incorporating exogenous nucleic acid into an in situ ocular cell, (b) the uptake of said exogenous nucleic acid, and (c) the expression of said exogenous nucleic acid, to the recited preamble "treating a genetic ocular disease".

In claims 13, 22 and the dependent claims, it is unclear what is encompassed by the term "treating" since it is not clearly defined in the specification. Does treating encompass stabilizing or slowing the decline of a genetic ocular disease? Or does it encompass only in an improvement of symptons associated with the disease, and which symptons? Clarification is requested because the metes and bound of the claims can not be clearly determined. Also in claim 22, the phrase "said disease is lysosomal storage disease" is unclear. How can an ocular disease is also a lysosomal storage disease? Clarification is needed.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 13-22 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims (6, 9-12 and 15-19) of copending Application No. 09/018599. Although the conflicting claims are not identical, they are not patentably distinct from each other because the scope of a method for treating a genetic ocular disease or an ocular disease in the instant application is encompassed within the scope of a method for treating ocular disease in the copending Application No. 09/018599.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Conclusions

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Quang Nguyen, Ph.D., whose telephone number is (703) 308-8339.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Karen Hauda, J.D., may be reached at (703) 305-6608.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-2801.

To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1632.

Papers related to this application may be submitted to Group 160 by facsimile transmission. Papers should be faxed to Group 160 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15,1989). The CM1 Fax Center number is or (703) 305-3014 or (703) 308-4242.

Quang Nguyen, Ph.D.
Examiner, AU 1632

Karen M. Hauda
KAREN M. HAUDA
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600